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Primary Immune Thrombocytopenia in Children: Experience of Pediatric Hematology and Oncology in Casablanca

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Abstract **Original Research Article**

Introduction: The primary immune thrombocytopenia (ITP) of the child is an autoimmune disorder characterized by isolated thrombocytopenia; it is a benign pathology of evolution most often favorable. ***Purpose:*** To describe the epidemiological, clinical, therapeutic and progressive characteristics of childhood and adolescent ITP in the pediatric hematology and pediatric oncology unit in Casablanca. ***Patients and methods:*** We conducted a retrospective descriptive study from January 2010 to December 2016, collating the records of patients followed for ITP whose age is less than or equal to eighteen years. We studied epidemiological, clinical, biological, therapeutic and evolutionary data. ***Results:*** 52 patients were included in this study. The median age at diagnosis was 9 years. The sex ratio M / F: 0.33. Hemorrhagic manifestations were the revealing syndrome in 92% of patients with a sudden onset in 73% of patients. The average platelet count was 16,000 / mm³. 88.5% of patients were initially treated with corticosteroid alone, and 11.5% withheld and monitored. ITP was acute in 27 patients (52%) and persistent or chronic in 25 patients (48%). For the treatment of chronic or persistent forms Rituximab was used in 11 patients (21%), and splenectomy was performed in 10 patients (19%). ***Conclusion:*** ITP is a common pathology in children whose evolution is most often favorable, spontaneously or with first-line treatments. However a progression towards a chronic or persistent ITP is possible, higher in our series, raises other modalities of the treatment.

Keywords: Primary immune thrombocytopenia, Children, Response, Treatment.

INTRODUCTION

Primary immune thrombocytopenia (ITP) is an autoimmune disease, it defined by isolated acquired thrombocytopenia, the peripheral blood platelet count, must be less than 100G/L in the absence of any other identified cause and / or associated known disease; it can affect children and adults, this disease is heterogeneous in its pathophysiology, clinical features and responses to treatment. For children the evolution is often favourable.

The ITP represents one of the most common causes of symptomatic thrombocytopenia in children. It's due to an immunological disorder responsible for peripheral destruction of normal platelets by self-reacting antibodies with deficiency on platelet production [2]. The annual incidence of ITP is estimated at between 1 and 6.4 cases per 100,000 children [3, 4]. The evolution is often favourable with spontaneous healing reported in about 50% of cases , the evolution towards chronicity is noted in about 20 to 25% of cases [5], mortality related to this pathology remains rare (less than 1%); often due to a serious hemorrhage such as cerebro-meningeal hemorrhage.

Clinical presentation is very variable, the gravity of bleeding is heterogeneous, and serious bleeding is not common if the platelet count is above 30 G/L. The most major form of bleeding can be represented by intracranial haemorrhage, is rare and is most often seen in older patients who have other comorbidities [6]. The yearly risk of fatal haemorrhage is around 1.6–3.9% [7], this risk varies with age, higher for adults.

ITP on children and adults is not quite the same; there is some difference on the physiopatology and clinical outcome. In children, ITP can be preceded by a viral infection or immunisation. In most Children the disease remits spontaneously by 6 months with little need for medical treatment.

The therapeutic strategy is adapted to the severity of the haemorrhagic syndrome and / or the

depth of thrombocytopenia. The proposed treatments aim to either reduce the destruction of platelets (immunosuppressant, splenectomy); or to enhance platelet production by thrombopoietin receptor agonists (ARTPO) [8]; most recently used.

The aims of our review are to describe the epidemiological, clinical, therapeutic and progressive characteristics of ITP in children and adolescents followed in the paediatric clinical haematology and oncology department of Casablanca, and discuss our results that remain satisfactory overall despite the unavailability of expensive treatment

PATIENTS AND METHODS

This is a descriptive study of 52 cases of patients treated for ITP in the paediatric haematology and oncology department of the Ibn Rochd University Hospital Center in Casablanca, spread over a period of 7 years, from January 2010 to December 2016. The analysis of patients' files was done retrospectively.

The study included all patients under the age of 18 years, consulting for isolated thrombocytopenia revealed or not by cutaneous haemorrhagic syndrome (petechial purpura and / or ecchymosis), mucous or visceral haemorrhagic syndrome. Etiological assessment includes CBC, blood smear, haemostasis assessment, hepatic B and C serology, immunological assessment and sometimes bone marrow aspiration. It was excluded secondary thrombocytopenia to another pathology that is haematological or immunological. The severity of the ITP was evaluated based on the initial platelet count (<20000 / mm³) and the severity of the bleeding syndrome to establish the Buchanan Score.

First-line treatment with corticosteroid therapy was initiated in patients who had platelet counts ≤ 20000 / mm³ and / or had a bleeding syndrome. Completion of platelet counts after 2 or 3 weeks of initiation of treatment allowed for evaluation of the therapeutic response for each patient, defining three types of responses in the first line:

- Complete response (CR) if platelet counts> 100000 / mm³.
- Response (R) if platelet count 30000 and 100 000 / mm³ or at least doubled from baseline.
- No response (NR) if the platelet count <30000 / mm³ or a rate <twice the initial rate.

The evolution of the platelet counts and the therapeutic response allowed defining the three phases of the ITP according to the International Labor Group of 2009 (IWG):

• Newly diagnosed (<3 months).
• Persistent: between 3 and 12 months.
• Chronic evolving more than 12 months.

We collected the data on a pre-established form and then analysed the results using SPSS-type software.

RESULT

Epidemiological, clinical and biological data

Fifty-two patients were included in the study. The median age at diagnosis was 9 years (range 4 months to 18 years) with a clear female predominance 40 girls (77%) for 12 boys (23%). The seasonal distribution had shown a peak frequency in the spring (42.3%). The search for precipitating factors found a vaccination in 8% and a recent seasonal viral infection in 17% of patients.

The ITP installation mode was brutal in 73% and insidious in 27%. Regarding the clinical presentation, 92% of patients had haemorrhagic manifestations at the time of diagnosis, dominated by cutaneous haemorrhages (petechial or bruising) in 90% of cases, followed by gingivorragia in 19% of cases and epistaxis in 17% of cases. Cerebro-meningeal haemorrhage was reported in only one patient (Table 1). The mean number of platelets at the time of diagnosis was 16000 / mm³ with extremes ranging from 1000 / mm³ to 80000 / mm³, of which nearly 79% had a rate below 20000 / mm³. The blood smear performed in 84% of cases confirmed thrombocytopenia. The bone marrow aspiration was performed at diagnosis in 31 patients (60%), the marrow was rich in megakaryocytes without significant abnormality, advocating a peripheral origin of thrombocytopenia. The rest of the biological assessment which included haemostasis analysis, liver function, and hepatitic serology, excluded secondary thrombocytopenia. Some cases were diagnosed on the basis of typical clinical presentation and response to first-line therapy.

Treatment and evolution

For six patients (11.5%), therapeutic abstention with surveillance was the rule. The remaining patients had been treated with corticosteroids alone (88.5%). Prednisolone was the corticosteroid used in all patients; the first-line treatment consisted of an initial dose followed by a slow increase over 2 to 3 weeks. The evaluation of the response towards the 2nd-3rd week had objectified a complete response (platelets> 100000 / mm³) in 31% of the patients, a response with platelets between 30000 and 100000 / mm³) or having at least doubled the initial rate 39% while 30% of cases did not respond (Figure 1). The use of intravenous immunoglobulin (IVIg) was very modest; they were administered only to two patients; at a dose of 1 g / kg / day for 2 days (D1 and D3).

ITP was acute in 27 cases (52%) and persistent or chronic in 25 cases (48%). The risk factors for progression to chronic ITP were mainly age and gender (Table 2). For the treatment of chronic or persistent

forms, Rituximab was indicated in 11 patients (21%); at a dose of 100 mg / m² in 9 patients (17%) and 375 mg / m² in 2 (5%). The average duration between diagnosis and Rituximab was 301 days (range 65 days and 585 days). Rituximab was administered for 4 weeks with one injection per week. One response (R) was obtained in 3 patients (6%); all having received the dose of 100 mg / m². Seven patients (13,5%) had received a high dose of dexamathasone 0.6 mg / kg / day for 4 days at the time of hemorrhagic relapses, only one patient received Vinblatin. Splenectomy was performed in 10 patients (19%) after failure of other therapies.

The final status, with a median of follow-up of 27 months (range, 6 months to 71 months), showed that 43 (83%) were in remission, 7 (14%) had no remission; one patient was lost to follow-up after splenectomy (1.5%) and one patient death following cerebral haemorrhage (1.5%).

Table-1: Hemorrhagic manifestations at diagnosis

haemorrhagic manifestations	Number of cases (%)
Cutaneous haemorrhages	
• Petechial	34 (65%)
• Bruising	30(58%)
Mucous haemorrhages	
• Epistaxis	9 (17%)
• Gingivorragia	10 (19%)
Genital haemorrhage	4 (8%)
Gastrointestinal bleeding	1(1,9%)
Conjunctival hemorrhage	1(1,9%)
Cerebral hemorrhage	1(1,9%)

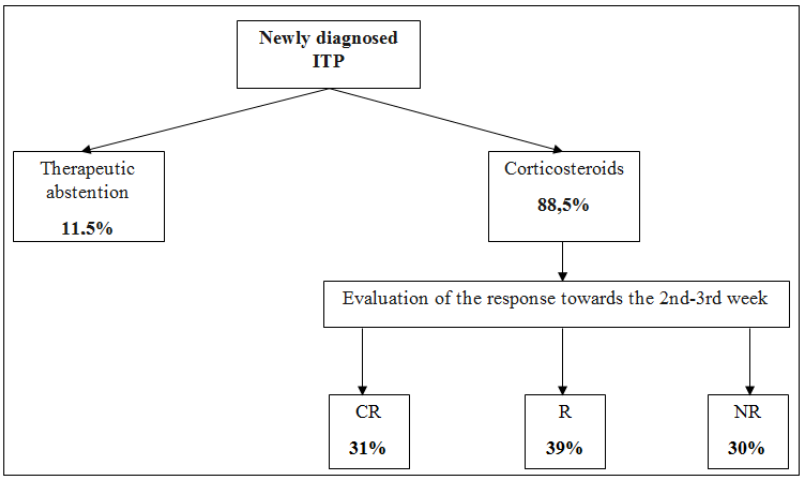

Fig-1: **Risk Factors for Passing ITP into Chronic Form (Our Study)**

CR: Complete response if platelet count> 100000 / mm³; **R**: Response if platelet count 30000 and 100 000 / mm³ or at least doubled from baseline; **NR**: No response if the platelet count <30000 / mm³ or a rate <twice the initial rate.

Table-2: Study of risk factors for progression to chronic ITP

Risk factors for progression to chronic ITP	Number of cases (%)
Age at the time of diagnosis	
≤6 years	7 (28%)
6-12 years	8 (32%)
>12 years	10 (40%)
Sexe	
Girls	19 (76%)
Boys	6 (24%)

DISCUSSION

The ITP of the child appears at any age. It is more common in the young male infant and adolescents. The paediatric peak is between 1 and 6 years of age [9]. In a study of 2031 children with acute ITP, the mean age at presentation was 5.7 years [10]. It affects both girls and boys without any predilection [11], however, we found a female predominance in our study, and this predilection was also reported by some authors like N. Mushtaq et al for Pakistan, [12] and LS faihi *et al.* for Tunisia [13].

For the seasonal distribution, we noticed a peak frequency during the spring, this has already been reported by several series in the literature [14,15].

Many differences exist between paediatric and adult ITPs in terms of their underlying pathophysiology and clinical outcomes. In children, ITP may follow a viral infection or immunisation. Predictive factors were found in our series in 25% of cases, either a vaccination (8%) or a recent seasonal viral infection (17%), both factors were reported as predictors of I TP with rates ranging from 27% to 62% [16-18].

In children, ITP often manifests brutally (73% in our series), by cutaneous haemorrhages: ecchymosis and petechial eruptions; and haemorrhages of the mucous membranes: gingivorragia and epistaxis, in the majority of cases [17], this is usually accompanied by severe thrombocytopenia <20000 / mm³ [19]; some patients present with more severe haemorrhages, such as menorrhagia and rectal bleeding, which can sometimes be life-threatening, especially in the case of intracranial haemorrhage (ICH), which is the most serious complication.

Bleeding in ITP is characterizes by heterogeneity, unpredictability, and likely based on a composite of risk factors [20]. Because of this, no evidence-based validated risk stratification.

Precise clinical history, complete physical examination, complete blood count analysis, and blood smear are key elements in the diagnosis of ITP of the child [21]. The realization of the bone marrow aspiration is not necessary for children who have recently been diagnosed with ITP [22], however, it is the only way to eliminate acute leukemia in the presence of thrombocytopenia [18]. Bone marrow aspiration is obligatory in front of any atypical presentation of ITP: splenomegaly, prolonged fever, bone pain, unexplained anemia, associated cytopenia, ITP refractory to usual therapies (IVIg or corticosteroids), or before splenectomy [21]. In our series the bone marrow aspiration was performed in most of our patients (52%), at diagnosis, this rate remains high compared to that reported in the literature and which varies according to the studies between 30 and 40% [11, 15, 23].

Children tend to have high spontaneous remission rates and low likelihood of disease recurrence or chronicity. Therapeutic observation and abstention is the rule for newly diagnosed ITP; however, it is necessary to initiate first-line treatment in the event of a severe bleeding syndrome (evaluated with a Buchanan score> 2), regardless of platelet count or if the platelet count is less than 10,000 / mm³, or in case of a threatening hemorrhagic syndrome [18]. These treatments are intended to quickly raise platelet levels. Initiation of treatment with a platelet count <20 000 / mm³ is not unanimous.

The first-line treatment of choice in newly diagnosed ITP, if indicated, is corticosteroid therapy, different regimens are proposed, but the most widely used in our unit is oral Prednisone for 21 days at a dose of 1 at 2 mg / kg (up to 60 mg / day) and rapid decay [18], at this dose a significant rise in platelet counts is observed during the first week, and normalization in 7 to 25 days at 60 % patients. High dose corticosteroids are reserved for severe forms.

As for IVIg, given at a dose of 0.8-1g / kg / day, they cause a response in more than 80% after 1-2 days [18, 24]. But their high cost associated with immediate side effects (headache, vomiting, nausea, fever) and infectious risk, encourages us to recommend second-line after failure of corticosteroids or in case of severe ITP.

Children the disease remits spontaneously by 6 months with little need for medical treatment. Around 15% of children will go on to develop chronic ITP.

The progression to chronic or persistent ITP was noted in our serie in 48% of patients. This rate is significantly high compared with other series in the literature (14.5% to 32.8%) [13, 18, 23]. This is related to two risk factors for chronicity that were identified in our serie: advanced age at diagnosis and female gender.

The decision to treat these forms is largely based on the frequency and severity of bleeding and the impact on quality of life (absenteeism, depression, hospital travel). First-line treatments may be used as needed to prevent bleeding, especially during the first 12 months of the persistent phase of the disease, pending a possible spontaneous remission.

The use of anti-CD20 (Ritixumab) is proposed for persistent and chronic forms of ITP with significant continuous bleeding despite first-line treatments, it can also be considered as an alternative to splenectomy in children and adolescents with chronic ITP or in patients who do not respond favourably to splenectomy [21]. This treatment makes it possible to obtain an early response in 60% of the cases and a prolonged remission in 40% [25], with a good tolerance. The proposed dose is 375mg / m², 4 weekly injections, but it is possible

that lower doses are sufficient to provide immunosuppression and induce a platelet count response [26]. A nonrandomized trial provided low-dose rituximab, 100 mg weekly for 4 weeks, upfront in treatment-naive patients [27].

In our context, and because of the very limited availability of Rituximab, few patients in our series were able to benefit from this treatment, and for the majority a reduced dose was favoured.

The use of high dose dexamathasone 0.6 mg / kg / day for 4 days was also used for these forms with significant bleeding but is proposed in chronic forms as an alternative to splenectomy or in case of no response [18]. In our series only seven patients received dexamethasone in the second line.

Splenectomy is no longer the standard treatment for chronic or persistent ITP, but it can cure 70 to 80% of patients according to the series. According to the recommendations of the Severance group, it is only offered from the age of 5 years. Currently, its indication is increasingly limited since the use of Rituximab and thrombopoietin receptor agonists that have proven effective since 2006, they act by stimulating, in a dose-dependent manner, platelet production [8].

Recently, there are two US Food and Drug Administration (FDA)- approved thrombopoietin receptor agonists TPO-RAs, eltrombopag and romiplostim. These agents have both been extensively studied in adults and children with chronic ITP. This treatment remains expensive and not accessible in our context.

Even our limited ressources our results seems to be favourable, The final status, with a median of follow-up of 27 months (range, 6 months to 71 months), showed that 43 (83%) were in remission, only 7 (14%) had no remission.

CONCLUSION

ITP is a benign pathology, often of favourable evolution but presenting a real challenge for practitioners. The treatment is indicated in case of hemorrhagic syndrome or deep thrombocytopenia, mainly by corticosteroids alone or in combination with intravenous immunoglobulins, although in our serie, the use of IVIg is very modest because of the high cost. It is noted that the evolution towards a chronic or persistent ITP in our series is higher compared to what has been described in the literature.

Despite the limited resources and the difficulties of access to expensive treatment, our results remain satisfactory overall. Recently, according to recomandations, we tend to reduce doses of steroids and reduce exposure period to steroids.

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